Highlight Review

Organometallic iridium arene compounds: the effects of *C*-donor ligands on anticancer activity

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Abstract

In the past decade, libraries of iridium organometallic arene compounds have expanded rapidly, with the majority of their applications aimed towards effective catalysts and potential anti-cancer drug candidates. Researchers have begun to adapt the traditional "piano-stool" structures to include different bidentate ligands, ancillary ligands and extend the aromaticity and functionality of the arene substituent, all in the hope to optimize their activities and allow the determination of structure activity relationships. Many of the complexes incorporate *N*- and *O*-donor ligands, but more recently, these structures have been expanded to include *C*-donor ligands such as cyclometalated bidentate ligands and *N*-heterocyclic carbenes. This mini-review highlights the recent and ongoing research in *C*-donor iridium arene complexes, and discusses their importance as potential anticancer drugs.

Introduction

The medicinal uses of metals have been reported for almost 5000 years, where in around 3000 BC Egyptians used copper to sterilize water, in 2500 BC Ancient China and Arabia used gold-based medicines and in around 1500 BC the Egyptians were reported to use iron and zinc remedies to promote the healing of wounds.[1] However, the use of metals in medicinal chemistry was neglected until the 1900s, when potassium dicyanoaurate (**Figure 1**, **1**) was first reported for its use in tuberculosis, and a small number of compounds were reported for their leishmaniasis (disease caused by parasites of the Leishmania type) and antibacterial activities. In 1909, Paul Ehrlich first discovered the antisyphilitic activity of the drug arsphenamine (Salvarsan), an arsenic containing compound, (**2**).[2] This organoarsenic compound was the first modern chemotherapeutic agent, however, it was thought to contain an As=As double bond, until 2005, when after extensive mass spectrometric analysis, the structure was confirmed to have As–As single bonds and exist as a mixture of cycloarsenic rings, with three and five arsenic centres.[3] It was not until 1952 when Dwyer reported the bacteriostatic and bactericidal activity of cobalt and ruthenium compounds,[4] that the field of bioinorganic chemistry began to rapidly expand.

There have been only few major breakthroughs in the use of metals in medicine, and this work stemmed from the discovery of the unexpected therapeutic effects of cis-diamminedichloridoplatinum(II) (cisplatin or CDDP) (CDDP, **3**). This compound was first described by Michele Peyrone in 1845 and known as Peyrone's salt,[5] though it was the work by Rosenberg *et al.* in 1965 that brought CDDP into the spotlight.[6,7] The group were studying electrolysis, when it was noted that the platinum electrodes generated a platinum species which arrested the cell division of *Escherichia coli* (*E. coli*). The square planar compound, *cis*-$[PtCl_2(NH_3)_2]$, was later found to be effective at inhibiting the development of mass sarcomas in rats, and after several clinical studies it was approved for use in ovarian cancers, and the Food and Drug Administration (FDA) approved it in 1978 as Platinol®. To date, this compound is the most effective inorganic compound in the clinic, and is still used in the treatment of ovarian, testicular, lung and bladder cancers, as well as lymphomas, myelomas and melanoma.[8] However, CDDP is well documented to be non-specific for cancers and its continued use is greatly inhibited by dose limiting side effects and intrinsic or acquired drug resistance.[9–11] Such aspects sparked research towards new platinum-based therapeutics, which have lower toxicity towards normal cells types and can treat CDDP-resistant tumors. Although the platinum metal compounds make up the majority of the metal drugs within the clinic, much research has been aimed towards new transition metal compounds with lower cytotoxicity towards normal cell types.

Organometallic arene compounds are metal complexes containing at least one metal-carbon bond and/or an arene substituent. This class of compounds have shown much promise in the quest for new anticancer compounds, as unlike many of the platinum complexes, the use of organometallics offers a greater range of structural design, diverse stereochemistry and by effect ligand design can provide control over the kinetic properties.[12] Organometallic complexes such as metallocenes, half-sandwich complexes, carbenes-, and both CO- and π-ligands have been widely studied for many transition metals.[12] After the discovery of the well-known ruthenium compounds,

NAMI-A (**4**) and KP1019 (**5**),[13–15] many ruthenium organometallic arene complexes were reported,[16,17] and analogous iridium complexes were designed based on their structures. After platinum, the ruthenium libraries have been the largest class of metal-based compounds studied, and it has only been in the past 10 years when the therapeutic potential of iridium organometallic complexes have been become apparent.[18,19] Iridium(III) is often considered one of the most inert metal ions, partly due to the reported inert nature of the low-spin d^6 metal ion, with the water ligand exchange of $[Ir(H_2O)_6]^{3+}$ reported to take hundreds of years,[20] whilst $[Cp^*Ir(H_2O)_3]^{2+}$ is approximately 10^{14} times faster.[21] This is potentially important and desirable for drug design. The ligands surrounding the iridium metal ion play a large role in the compound's stability and may be of importance to the biological targeting.[22]

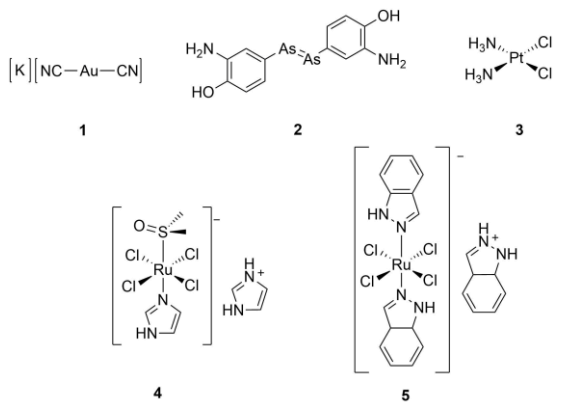


Figure 1. Structures of early inorganic therapeutics **1**-**2** and the most prominent inorganic drug cisplatin (CDDP) **3**, and prominent drug candidates NAMI-A **4** and KP1019 **5**.

There have been numerous reports of both iridium(I) and iridium(III) complexes containing *N*-,[23–50] *O*-,[51–61] *P*-[62–65] and *S*-donor[66–71] ligands, dimeric species,[33,72,73] mononuclear scaffolds[74–79] and sandwich complexes,[80–82] which have shown significant potential in the quest for new anticancer therapeutics. There have been several reviews on non-arene iridium complexes which incorporate a range of C-donor ligands,[19,83] however, due to the increased focus on iridium arene complexes over the past 5 years, this review will highlight this emerging research fields of cyclometalated and *N*-heterocyclic carbene iridium arene complexes as potential drug candidates.

Iridium(I) compounds

The first organometallic iridium compounds to be reported for their therapeutic activity were d^8 iridium(I) complexes [Ir(COD)(acac)] (**Figure 2**, **6**) and $[IrCl(COD)]_2$ (**7**) (COD = 1,5-cyclooctadiene, acac = acetylacetone).[84,85] in which these square planar structures are similar to that of CDDP. Along with its rhodium analogues, these compounds were proven to be effective in the inhibition of subcutaneous tumor growth, however, they had low effects on lung metastases.[86] The findings were attributed to the rapid oxidation to the kinetically inert iridium(III), which leads to its inactivation. However, when tested in mice bearing Ehrlich ascites, compound **6** gave 100% cures and inhibited growth of subcutaneous Lewis lung carcinoma in mice, whilst compound **7** showed anti-metastatic activity in the Lewis lung model, but no inhibition of primary tumors.

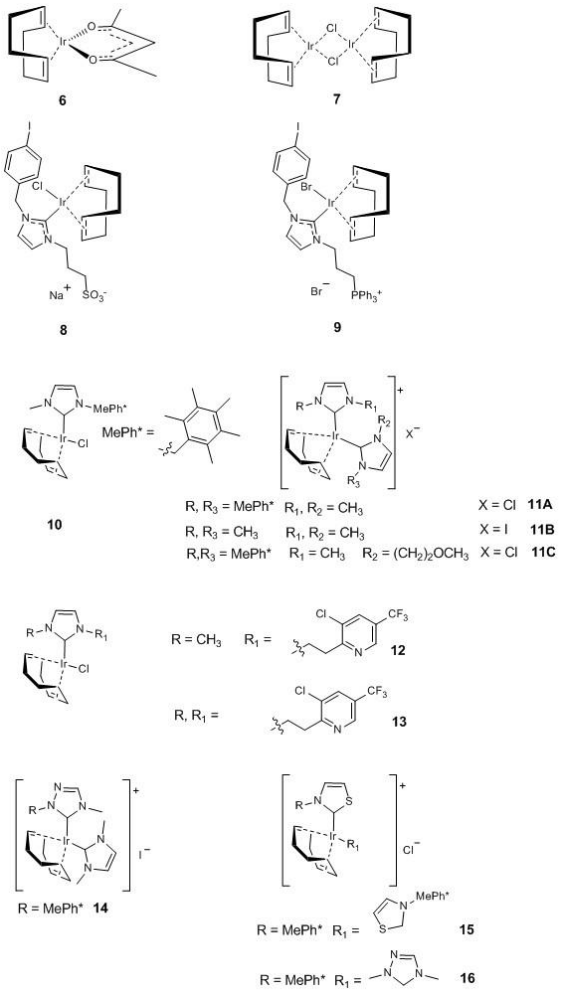


Figure 2. Promising iridium(I) *N*-heterocyclic carbenes **6**-**16**.

More recently, research has been aimed at changing the bidentate ligands to include *N*-heterocyclic carbenes (NHCs). This is mainly due to the neutral nature of the ligands, which allows for both charged complexes to be formed, as well as the ability to stabilize low oxidation state iridium. This work began in 2013 when Simpson *et al.* synthesized a range of iridium(I) NHC compounds containing sulfonate or phosphonium groups (**8** and **9**).[87] The compounds bearing a terminal phosphonium group (**9**), which has properties of delocalized lipophilic cations, showed a > 4-fold increase in activity against breast adenocarcinoma (MDA-MB 231, IC_{50} values = 24 to 30 μM), when compared to the sulfonate analogues (IC_{50} values >100 μM). However, the same compound is equitoxic against normal mouse fibroblasts (L929). Additionally, the cationic complexes exhibited low minimum inhibitory concentrations (MIC) against a range of bacteria, and an evaluation of the cellular metal accumulation clearly suggested a positive contribution of the phosphonium group, with peptides suggested as the cellular targets.

In 2015, this work of iridium(I)-NHC complexes was extended by Gothe *et al.*, who highlighted a new neutral iridium(I) COD compound which incorporated a bulky NHC substituent (**10**).[88] This compound exhibited only moderate activity against both breast adenocarcinoma (MCF7) and colorectal adenocarcinoma (HT-29, IC_{50} values = 14 to 19 µM), but also full inhibition of normal human embryonic kidney cells, (HEK-293T) at 30 µM. Importantly, the compound formed adducts between cytochrome *c*, due to a loss of the ancillary chlorido ligand and a simultaneous oxidation of the Ir(I) to Ir(III). In 2016, the group extended the library to include *bis*-carbene complexes (**11**).[89] These cationic complexes show more promise and higher activities, with complexes **11A-C** all active in the high nanomolar range (IC_{50} values = 0.49 – 0.61 µM (MCF7) and 0.26 – 0.47 µM (HT-29). Unlike the neutral complexes, which undergo rapid hydrolysis, the cationic complex has a high stability towards oxidation and only slow oxidation from Ir(I) to Ir(III) was observed in an excess of H_2O_2, and showing that the antiproliferative effects are not related to hydrolysis. Unlike the previously reported compound **10** which binds to cytochrome *c* and lysozymes by oxidation to Ir(III), the cationic complexes show no reaction with proteins. Alongside these new classes of complexes, work by Maftei *et al.* highlighted asymmetric (**12**) and symmetric (**13**) neutral iridium(I)-NHC trifluoromethylpyridine derivatives which surprisingly have no cellular activity, and IC_{50} values against all 12 cell lines were > 100 µM.[90] More recently, triazole and thiazole-derived iridium(I) NHC complexes have emerged, (**14-16**)[91] and exhibit significant interactions with model proteins and hexameric oligonucleotide ODN1. This highlights the necessity of fine-tuning of the ligand environment and a need to investigate structure-activity relationships. There continues to be ongoing research in the field of iridium(I) compounds as potential therapeutics, however, it appears their stability towards oxidation could remain an issue in further *in vitro* and *in vivo* assays. Thus, a significant proportion of iridium research has been aimed towards iridium(III) drug candidates.

Iridium(III) compounds

i) Cyclometalated *C*-donor complexes

Most of the iridium(I) work incorporates COD moeties and there have been only few reports on iridium(III) COD complexes. To date, these complexes containing *N*,*N*-bidentate ligands and have yet to be expanded to include cyclometalated ligands or NHCs.[92–94] The main library of cyclometalated iridium complexes are based on the work by Sadler *et al.*, where they have synthesized libraries of anionic *C*,*N*-donor ligands which are analogous to their previously published neutral *N*,*N*-donor ligands. Lui *et al.* first published and developed iridium(III) complexes containing neutral *N*,*N*-chelated bpy (bpy = 2,2'-bipyridine) and the analogous anionic *C*,*N*-chelated ligands (**Figure 3**, **17** and **18**), and showed for the first time that the iridium(III) *C*,*N*-donor complex was > 9-fold more cytotoxic against human ovarian cancer (A2780) when compared to the *N*,*N*-donor complex, which remained inactive.[95] Both of these complexes exhibit rapid hydrolysis in water and the *C*,*N*-complex has significant binding to 9-EtG and 9-MeA (96% and 86% respectively), whereas the *N*,*N*-complex exhibits only moderate binding to 9-EtG (61%) and no binding to 9-MeA. Importantly, the group were the first to obtain single crystal X-ray diffraction data for the *C*,*N*-complex with 9-EtG, showing binding at the N7 position of guanine (**18A**), highlighting their potential modes of action by DNA binding. Further work introduced functionality to the cyclopentadienyl moiety, Cp^x (where x = Me, ph or biph (**19B**)), to increase the hydrophobicity and the ability of the systems to intercalate with DNA.[96] The complexes again undergo rapid hydrolysis and the active aqua adduct is the major form after hydrolysis at physiological pH. Above pH 8.7, the *C*,*N*- complexes form hydroxo-bridged dimers (**19C**), suggesting that they are less stable towards hydrolysis than the *N*,*N*- analogues.

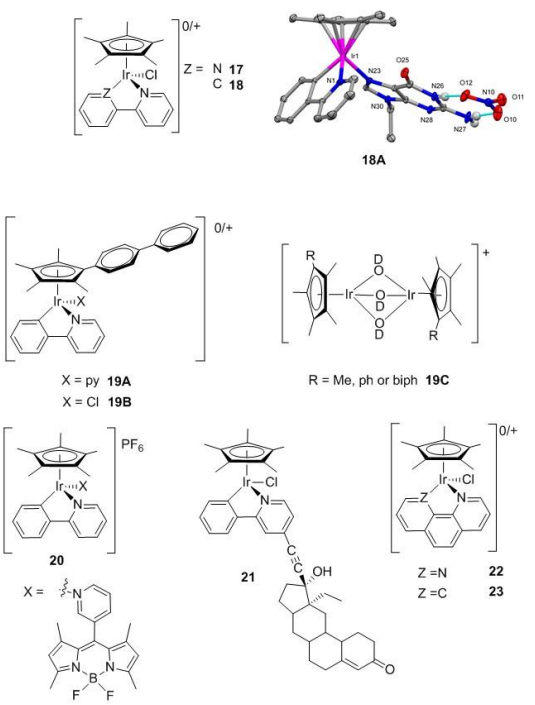
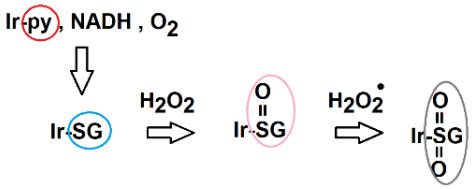


Figure 3. Selected iridium(III) *N*,*N* and *C*,*N*-donor complexes **17-23** (the crystal structure is reproduced from the publications by Liu *et al.*,[95] with hydrogen atoms and solvent molecules omitted for clarity)



Scheme 1 Pyridine complex **19A** forms a glutathione adduct Ir-SG, which is oxidized by H_2O_2 to the sulfonato complex Ir-S(O)G and sulfinato complex Ir-$S(O)_2$G (Liu and Sadler *et al.*[97])

It has been shown that both electronic and steric properties of the bidentate ligands can have a large effect on the chemical and biological activities,[96,98,99] with electron-donating groups showing the largest increase in anticancer activity.[100] Amongst others, complex **18** was studied for its interaction with calmodulin, a calcium-binding protein found in the cytoplasm of all eukaryotic cells.[101] The degree of binding was elucidated by electron-capture dissociation (ECD)-based tandem mass spectrometry, and fragments were observed for MET (tyrosine kinase receptor) binding, although the strength of binding was relatively weak. This is the first mass spectrometry evidence of iridium(III) and its coordinative binding and the location of

protein binding sites. Additionally, unlike CDDP which binds and displaces all four monodentate ligands, the iridium complexes do not readily lose the Cp^x moiety of the chelating ligand.

Extensive studies have been conducted using Cp^{biph} iridium *C,N*-complexes which have a variety of benzyl and pyridine functionalities[99] and labile Ir-X ligands,[100,102] whereby the pyridine complex **19A** showed the highest potency and exhibits nanomolar activity.[22] The NCI 60 results show comparable or higher activity than the clinical drugs oxaliplatin (OXA) and CDDP, with complex **19A** being 6-13 times more active than CDDP. This complex was also the first iridium species shown to generate high levels of reactive oxygen species (ROS) in cancer cells, and is 13 times more potent in cancer cells when compared to normal cells human lung fibroblast cells (MRC-5).[103] Interestingly, the accumulation in ovarian cells (A2780) after just 24 hours was 20 times higher for complex **19A** when compared to the analogous chloride complex **19B**. Though the reaction with glutathione (GSH) was faster with **19B**, the pyridine complex **19A** formed a glutathione adduct Ir-SG, and due to the slower reaction it led to less deactivation of the complex. When the coenzyme NADH (2 equiv.) was added to a solution of Ir-SG, the NADH was oxidized to NAD^+ and ~ 34% of the Ir-SG complex was oxidized to the sulfonato complex Ir-S(O)G.[97] Following their previous catalytic studies of iridium and NADH to produce H_2O_2,[103] the group reported that the H_2O_2 is indeed responsible for the oxidation to Ir-S(O)G and in excess H_2O_2 the complex oxidized further to the sulfinato complex, Ir-$S(O)_2$G (**Scheme 1**).

More recently, analogous complexes of **18** were synthesized to incorporate BODIPY moieties in the ancillary ligand position, whereby complex **20** not only exhibited high quantum yields, but had high potential against a range of cell lines.[104] In particular this complex was more hydrophobic and 25 times more active than complex **18** against human ovarian cell line A2780. The addition of BODIPY allows for a more complete understanding of the cellular uptake, accumulation and distribution within the cells by using the complex's excellent photophysical properties, which in turn could provide further mechanistic understanding of both platinum and non-platinum drug candidates. Complex **20** exhibits a sharp absorption peak at 505 (ε = 74 900 M^{-1} cm^{-1}), and a fluorescence emission band at 514 nm, which is similar to free meso-pyridyl-BODIPY ligands. There was a small amount of photodissociation and photobleaching observed, but to a lesser extent than is observed for mono pyridine-based ligands. Upon incubation with MDA-MB-231 cells, fluorescence emission was observed, with small spots visible in the cells cytoplasm, giving evidence that the compound was able to permeate the cell. Due to the photostability of these BODIPY complexes, the uptake was measured in live cells, and reached maximum emission intensity in just 90 seconds. This work highlights the significant potential fluorescent molecules and probes can have on the understanding of the compounds' modes of action.

Along with the rhodium analogue, an iridium(III) steroidal complexes containing LEV-ppy (2-phenylpyridyl-4-ethynyl]-19-nortestosterone, **21**) was synthesized and exhibited ~6-fold high potency against human breast cancer cell line (T47D) than CDDP and was approximately twice as active as the non-steroidal analogue.[105] The complexes also had higher potencies against the CDDP resistant ovarian cancer cell line (A2780cis), with resistance factors ranging 0.9-1.1. Unlike CDDP, which remains only moderately cytotoxic against this cell line, this complex has a high resistance factor of 15.7. These complexes interact with CT-DNA and are cathepsin B inhibitors.

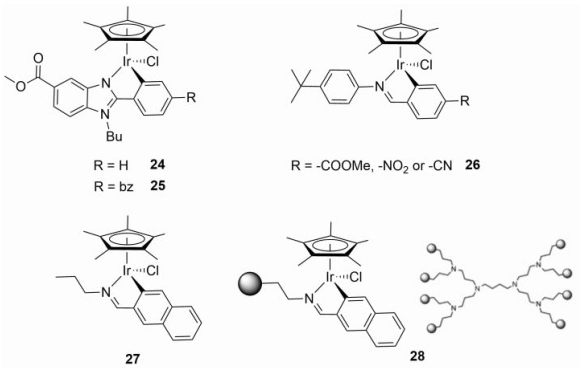


Figure 4. A range of cyclometalated benzimidazole and Schiff base complexes **24-28**

The cyclometalated bidentate *C,N*-ligands have been extended to include functionalized arene rings,[99,102] reports by Novohradsky *et al.* showed that the neutral *N,N*-compound **22** are inactive (IC_{50} > 100 μM) against ovarian and breast carcinomas, whereas the cationic *C,N*-compound **23** exhibited potency similar to CDDP against the ovarian cell lines, A2780 and A2780cis.[106] Upon assessing the cellular accumulation, it was noted that energy-passive diffusion plays a significant role, and the amount of uptake was enhanced by the depletion of intracellular ATP.

A range of *C,N*-cyclometalated benzimidazole compounds have been shown to have good activity against a range of cell lines, with compound **24** (**Figure 4**) exhibiting > 9-fold increase in potency when compared to CDDP (HT-29; IC_{50} (**24**) = 0.98 ± 0.02 μM and IC_{50} (**CDDP**) = 9.5 ± 0.2 μM).[107] Compound **24** displays *ca*. 2–3 more metal accumulation than that found for CDDP.[108] The complexes also induce high levels of apoptosis, S-phase cell arrest, strong binding to HSA and also weakly bind to DNA at the minor groove. This library was extended to include different R substituents, whereby the benzyl group, **25**, showed increased potency against a range of cancer lines.[109] However, the ruthenium p-cymene analogues remained more active than the analogous iridium compounds.[109] Compound **21** increased the degree of ROS in A2780 cells (at 2 mM), though the metal content in nuclear DNA was low.

Iridium(III) Cp* complexes containing functionalized Schiff base benzylidene ligands (**26**) have been reported, with complexes exhibiting effective binding to DNA either through intercalation and/or electrostatic interactions or through the display of covalent bonds.[110] With the addition of computational docking, it was found that these compounds bind within the minor groove of DNA, by insertion of the imine into a range of hydrophobic residues, through electrostatic interactions. The complex with a methoxy substituted ligand exhibited high nanomolar potency against chronic myelogenous leukemia, K562 (IC_{50} = 0.26 μM), with apoptosis studies showing an induction of apoptosis and an increase in ROS on decreasing MMP (mitochondrial membrane potential).[111] On analysis of the gene expression when K562 cells were treated

with this complex, there was an upregulation of Bax and caspase-9 and a downregulation of Bcl-2 and release of cytochrome *c*, all suggestive of apoptosis through intrinsic mitochondrial apoptosis pathways.

Additional adaptations were made of the benzylidene ligand to include naphthyl (**27**), which showed high activity against human ovarian carcinomas (A2780 and A2780cis) and remaining relatively non-toxic towards human embryonic kidney (HEK) cells. These systems were extended into poly(propyleneimine) dendrimer scaffolds in which the octanuclear chelating iridium metallodendrimer (**28**) shows superior activity in cancerous cells, when compared to the analogous mononuclear complexes **27**, however, they remain cytotoxic towards normal cell types.[112]

Sadler *et al.* have conducted research on the effects the arene substituent has on the systems. Interestingly, the cytotoxic values usually follow a trend, whereby the number of phenyl rings attached to the Cp^x moiety increases the activity, Cp^{biph} > Cp^{ph} ≫ Cp*. Liu and Sadler have reviewed these trends, and clearly show that increase in hydrophobicity of complexes leads to increased cell entry, higher *in vitro* activity, a higher degree of intercalation with DNA and a high K_{eq} for hydrolysis.[22] Therefore, modifications of the previously described complexes could increase the complexes' cellular activities and aid in more effective drug development.

ii) Carbene *C*-donor ligands

Though much work is being conducted on iridium(I) NHCs, the work on iridium(III) NHCs has only just been emerging within the last five years. To date four classes exist, which are (i) monodentate *C*-, (ii) bidentate *C,C*-, (iii) heteronuclear *C,N*- and (iv) *C,O*-donor ligands, of which a selection are shown in **Figure 5**. The first class of monodentate iridium(III) were synthesized in 2016, Schmitt *et al.*, in which they reported histidin-2-ylidene **29** and imidazol-2-ylidene **30**, however, the library of iridium complexes were non-toxic against all cell lines tested.[113]

The second class are the bis-carbene complexes, of which the first were reported in 2017 by Wang *et al*.[114] Eleven new complexes showed good anticancer activity, with several complexes exhibiting equitoxic potency when compared to CDDP against human cervical cancer cells, HeLa. Also, when the arene ring is Cp^{biph} and the imidazole functional groups included butyl (**31A**) or phenyl (**31B**), the complexes were 2.2- and 2.5-fold more potent than CDDP, respectively. The complexes undergo hydrolysis, and the slower hydrolysis was linked to potency. They also display no binding to 9-EtA and 9-EtG, yet they showed apoptosis, and several complexes inhibited the cell cycle in the G1 and G2/M phase whilst inducing high levels of ROS. Of the class of *C,C*-donors, Han *et al*. have reported functionalized phenyl NHC complexes which are all cytotoxic with complex **32** exhibiting high activity towards human lung carcinoma A549, which are 3-5-fold more cytotoxic than CDDP.[115] On analysis of the cell cycle, the complexes exhibit a disturbance in the sub-G1 or S phase, suggesting that these complexes have an effect on the growth cycle progression and can cause apoptosis, whilst inducing ROS. The subcellular localization in A549 cells was determined by confocal microscopy, and highlights an energy dependent mechanism of uptake.

Two reports have been made on iridium(III) imine-N-heterocyclic carbenes, with the first from Yang *et al*.[116] A range of complexes with varying alkyl and aryl derivatives have been synthesized and show high activities when tested against A549. In particular, complex **33** is > 10.7-fold more cytotoxic than CDDP, and has detectable fluorescence. No nucleobase binding was observed for all complexes, ruling out modes of action which involve DNA, though they reacted with GSH, catalyze the oxidation of NADH to NAD^+ and had moderate binding to BSA. Additional studies revealed a decrease in mitochondrial membrane potential and a disruption of the G2/M phase in the cell cycle, with an overall induction of apoptosis and the most active complex **33** also induced high levels of ROS. Upon analysis of the confocal images, complex **33** was found to enter the cells mainly by an energy-dependent pathway, and was located in the lysosome.

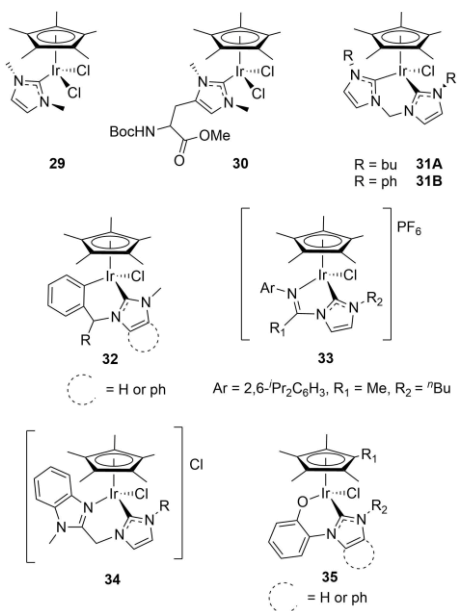


Figure 5. A range of N-heterocyclic carbene complexes **29-35**

Another library of complexes was reported by Han *et al*., which incorporate benzimidazole NHC ligands.[117] Complexes such as **34** were shown to exhibit activities up to 5-fold higher than CDDP when tested against A549 cells. As with the previous library of complexes, these benzimidazole complexes effectively bind with BSA, catalyze the oxidation of NADH to NAD+, and induce ROS which leads to apoptosis. They also target lysosomes and mitochondria, and enter the cell through an energy-dependent mechanism.

Lastly, the group of Zhang *et al.* designed a library of *C,O*-donor phenoxide chelated iridium(III)-NHC complexes (**35**), which show activity towards both A549 and cervical adenocarcinoma, HeLa.[118] The complexes hydrolyzed but displayed no binding to 9-MeA and 9-EtG and no cleavage to pBR322 plasmid DNA and showed only little binding affinity to CT-DNA. Like the *C,N* and *C,C* class of complexes, they interfere with $NADH/NAD^+$ hydrogen transfer and increase levels of ROS. Complexes were shown to either influence the cell cycle at the G0/G1 phase, or induce apoptosis and mitochondrial dysfunction. Only a small amount of binding to CT-DNA was observed, suggesting DNA is not a primary target, however, apoptosis and mitochondrial dysfunction was

observed, and may contribute to their activity against these cancer cells.

iii) Assemblies for delivery

Using the structure of complex **18**, cyclic peptide-polymer conjugates have been designed and synthesized (**Figure 6**, **36**), and provide a drug delivery system for the iridium(III) anticancer complexes. In 2018, Larnaudie *et al.* functionalized 2-hydroxypropyl methacrylamide (HPMA) by copolymerizing with a pyridine-containing monomer, which provided effective binding to the iridium metal center of complex **18**.[119] The copolymer was conjugated to self-assemble cyclic peptides to form nanotubes, and when tested against human ovarian cells A2780, they exhibit equitoxicity or increased toxicity compared to the free drug. The nanotubes also exhibit lower toxicity against normal human ovarian fibroblasts (HOF) when compared to the free drug. Upon analysis of the metal content inside the cells after equimolar incubation, the nanotubes and free drug exhibit similar percentages of metal, showing that the nanotube did not increase drug uptake, however, with the decrease in toxicity towards normal cell types, the nanotubes could provide a more efficient mode of action and could lead to improved delivery of inorganic drugs into the body.

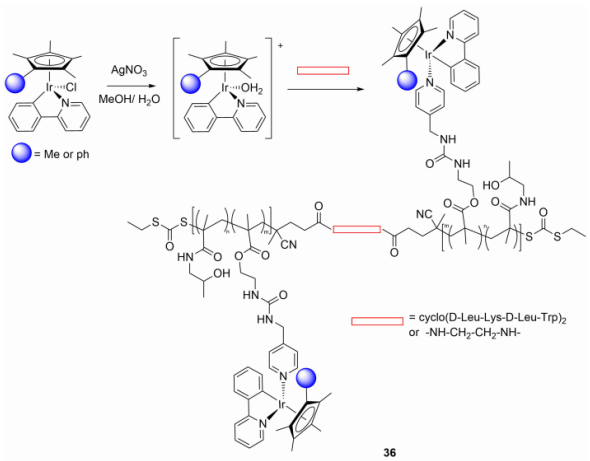


Figure 6. Cyclic peptide-polymer conjugates containing iridium(III) cyclometalated complexes, **36**

Conclusions

Though there are many interesting and effective iridium(I) complexes, their use as potential anticancer compounds is significantly limited by the oxidation of the complexes from Ir(I) to Ir(III). This change in oxidation state can cause the compounds to become inactive, or result in decomposition of the complex, making the therapeutic effects less pronounced. It can be concluded that iridium(III) compounds remain the most effective compounds, as their oxidation states are stable in aqueous medium, and the ease of synthesis allows for a more comprehensive library of compounds to be designed.

We have highlighted compounds with only a small range of cyclometalated and *N*-heterocyclic carbene ligands, however, there are numerous modifications which can be made to improve the cytotoxicity of these libraries. To date, there is no such *C*-donor ligand design which appears to be superior, though with the extensive work conducted on the anionic *C*,*N*-donor bipyridine analogues by Sadler *et al.* and their excellent *in vitro* potency, we believe these ligands to be the most effective ligand choice. Also, a key design feature which appears to be effective in increasing cytotoxicity is the addition of hydrophobic groups to the Cp^x ring. The most promising of all the substituents is the addition of a biphenyl (Cp^{biph}) ligand, in which the iridium compounds incorporating these ligands have generally shown a higher cellular uptake, increased ROS and exhibit nanomolar potency.

This review only highlighted two compounds which have been designed to incorporate anionic (sulfonate) and cationic (phosphonium) ligands, however, the cationic compound exhibits a > 4-fold increase in activity when compared to the anionic compound. These compounds are iridium(I) COD compounds, and cationic versus anionic studies have not yet been conducted for the iridium(III) *C*-donor compounds. Similar work has been reported on iridium(III) *N*,*N*-donor compounds, in which Zhang *et al.* have shown that changing the anionic counterion can exhibit up to a 9-fold increase in cytotoxicity.[101] This field of research could highlight new potential drug leads for the iridium(III) libraries, by incorporation of either cationic or anionic functional groups or changing the anionic counterion.

Two of the most promising features of drug design which have the potential to excel in clinic therapeutics are the use of fluorescent probes such as BODIPY and the encapsulation of the compounds into a polymeric design. The use of a probe can help to determine the cellular uptake and modes of action of the compounds, whilst the use of polymers can help to protect and stabilize the compound from degradation and deliver it to the active site within a cellular environment. Coupled together in one system, a fluorescent polymer which encapsulates iridium, or a polymer which encapsulates fluorescent iridium, are smart structural designs for the future of transition metal drug discovery and delivery, and will undoubtedly be a hot topic for future research platforms.

References and Notes

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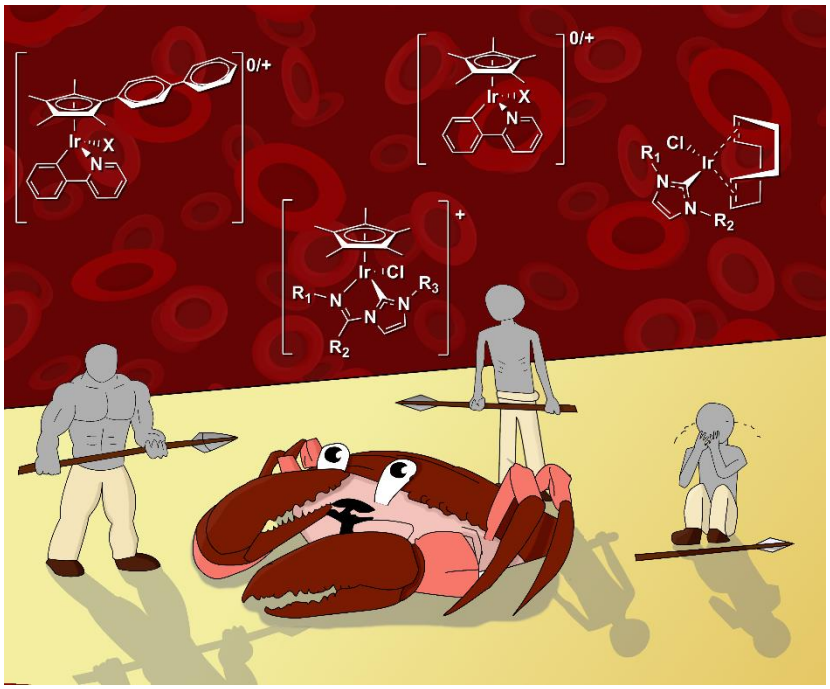
[1] C. Orvig, M. J. Abrams, Chem. Rev. 1999, 99, 2201–2204.
[2] P. Ehrlich, A. Bertheim, Berichte der deutschen chemischen Gesellschaft 1912, 45, 756–766.
[3] N. C. Lloyd, H. W. Morgan, B. K. Nicholson, R. S. Ronimus, Angewandte Chemie International Edition 2005, 44, 941–944.
[4] F. P. Dwyer, E. C. Gyarfas, W. P. Rogers, J. H. Koch, Nature 1952, 170, 190–191.
[5] M. Peyrone, Justus Liebigs Annalen der Chemie 1844, 51, 1–29.
[6] B. Rosenberg, L. Van Camp, T. Krigas, Nature 1965, 205, 698–699.
[7] B. Rosenberg, L. V. Camp, E. B. Grimley, A. J. Thomson, J. Biol. Chem. 1967, 242, 1347–1352.
[8] "Cisplatin - Drug Information - Chemocare," can be found under http://chemocare.com/chemotherapy/drug-info/cisplatin.aspx, n.d.

[9] J. T. Hartmann, H.-P. Lipp, Expert Opin Pharmacother 2003, 4, 889–901.
[10] J. Sastry, S. J. Kellie, Pediatr Hematol Oncol 2005, 22, 441–445.
[11] I. Arany, R. L. Safirstein, Semin. Nephrol. 2003, 23, 460–464.
[12] G. Gasser, I. Ott, N. Metzler-Nolte, J. Med. Chem. 2011, 54, 3–25.
[13] R. Gagliardi, G. Sava, S. Pacor, G. Mestroni, E. Alessio, Clin Exp Metast 1994, 12, 93–100.
[14] C. G. Hartinger, S. Zorbas-Seifried, M. A. Jakupec, B. Kynast, H. Zorbas, B. K. Keppler, J. Inorg. Biochem. 2006, 100, 891–904.
[15] E. Alessio, L. Messori, Met Ions Life Sci 2018, 18, DOI 10.1515/9783110470734-011.
[16] A. Levina, A. Mitra, P. A. Lay, Metallomics 2009, 1, 458–470.
[17] L. Zeng, P. Gupta, Y. Chen, E. Wang, L. Ji, H. Chao, Z.-S. Chen, Chem. Soc. Rev. 2017, 46, 5771–5804.
[18] Z. Liu, A. Habtemariam, A. M. Pizarro, S. A. Fletcher, A. Kisova, O. Vrana, L. Salassa, P. C. A. Bruijnincx, G. J. Clarkson, V. Brabec, et al., J. Med. Chem. 2011, 54, 3011–3026.
[19] C. C. Konkankit, S. C. Marker, K. M. Knopf, J. J. Wilson, Dalton Trans. 2018, 47, 9934–9974.
[20] A. Cusanelli, U. Frey, D. T. Richens, A. E. Merbach, J. Am. Chem. Soc. 1996, 118, 5265–5271.
[21] S. Cayemittes, T. Poth, M. J. Fernandez, P. G. Lye, M. Becker, H. Elias, A. E. Merbach, Inorg. Chem. 1999, 38, 4309–4316.
[22] Z. Liu, P. J. Sadler, Acc. Chem. Res. 2014, 47, 1174–1185.
[23] L. Guo, H. Zhang, M. Tian, Z. Tian, Y. Xu, Y. Yang, H. Peng, P. Liu, Z. Liu, New J. Chem. 2018, 42, 16183–16192.
[24] D. Kong, M. Tian, L. Guo, X. Liu, S. Zhang, Y. Song, X. Meng, S. Wu, L. Zhang, Z. Liu, JBIC, J. Biol. Inorg. Chem. 2018, 23, 819–832.
[25] N. R. Palepu, S. Adhikari, R. P. J, A. K. Verma, S. L. Shepherd, R. M. Phillips, W. Kaminsky, M. R. Kollipara, Appl. Organomet. Chem. 2017, 31, n/a.
[26] J. M. Hearn, I. Romero-Canelón, B. Qamar, Z. Liu, I. Hands-Portman, P. J. Sadler, ACS Chem. Biol. 2013, 8, 1335–1343.
[27] J. M. Hearn, G. M. Hughes, I. Romero-Canelon, A. F. Munro, B. Rubio-Ruiz, Z. Liu, N. O. Carragher, P. J. Sadler, Metallomics 2017, 10, 93–107.
[28] M. Gras, B. Therrien, G. Suss-Fink, A. Casini, F. Edafe, P. J. Dyson, J. Organomet. Chem. 2010, 695, 1119–1125.
[29] A. C. Matsheku, M. Y.-H. Chen, S. Jordaan, S. Prince, G. S. Smith, B. C. E. Makhubela, Appl. Organomet. Chem. 2017, 31, n/a.
[30] M. Kalidasan, S. Forbes, Y. Mozharivskyj, M. Ahmadi, Z. Ahmadihosseini, R. M. Phillips, M. R. Kollipara, Inorg. Chim. Acta 2014, 421, 349–358.
[31] R. M. Lord, A. J. Hebden, C. M. Pask, I. R. Henderson, S. J. Allison, S. L. Shepherd, R. M. Phillips, P. C. McGowan, Journal of Medicinal Chemistry 2015, 58, 4940–4953.
[32] S. J. Lucas, R. M. Lord, R. L. Wilson, R. M. Phillips, V. Sridharan, P. C. McGowan, Dalton Trans. 2012, 41, 13800–13802.
[33] S. J. Lucas, R. M. Lord, A. M. Basri, S. J. Allison, R. M. Phillips, A. J. Blacker, P. C. McGowan, Dalton Trans. 2016, 45, 6812–6815.
[34] Z. Almodares, S. J. Lucas, B. D. Crossley, A. M. Basri, C. M. Pask, A. J. Hebden, R. M. Phillips, P. C. McGowan, Inorg. Chem. 2014, 53, 727–736.
[35] L. He, K.-N. Wang, Y. Zheng, J.-J. Cao, M.-F. Zhang, C.-P. Tan, L.-N. Ji, Z.-W. Mao, Dalton Trans. 2018, 47, 6942–6953.
[36] L. He, Y. Li, C.-P. Tan, R.-R. Ye, M.-H. Chen, J.-J. Cao, L.-N. Ji, Z.-W. Mao, Chem. Sci. 2015, 6, 5409–5418.
[37] W. Ma, Z. Tian, S. Zhang, X. He, J. Li, X. Xia, X. Chen, Z. Liu, Inorg. Chem. Front. 2018, 5, 2587–2597.
[38] S. Adhikari, N. R. Palepu, D. Sutradhar, S. L. Shepherd, R. M. Phillips, W. Kaminsky, A. K. Chandra, M. R. Kollipara, J. Organomet. Chem. 2016, 820, 70–81.
[39] K.-G. Shyu, M. Velusamy, C.-W. Hsia, C.-H. Yang, C.-H. Hsia, D.-S. Chou, T. Jayakumar, J.-R. Sheu, J.-Y. Li, Int J Mol Med 2018, 41, 2589–2600.
[40] M. Ali Nazif, J.-A. Bangert, I. Ott, R. Gust, R. Stoll, W. S. Sheldrick, J. Inorg. Biochem. 2009, 103, 1405–1414.
[41] P. Starha, Z. Dvorak, Z. Travnicek, J. Organomet. Chem. 2018, 872, 114–122.
[42] R. P. Paitandi, S. Mukhopadhyay, R. S. Singh, V. Sharma, S. M. Mobin, D. S. Pandey, Inorg. Chem. 2017, 56, 12232–12247.
[43] S. Adhikari, D. Sutradhar, S. L. Shepherd, R. M. Phillips, A. K. Chandra, K. M. Rao, Polyhedron 2016, 117, 404–414.
[44] L. Tabrizi, Dalton Trans. 2017, 46, 7242–7252.
[45] M. Boege, C. Fowelin, P. Bednarski, J. Heck, Organometallics 2015, 34, 1507–1521.
[46] P. Govender, T. Riedel, P. J. Dyson, G. S. Smith, Dalton Trans. 2016, 45, 9529–9539.
[47] A. Kumar, A. Kumar, R. K. Gupta, R. P. Paitandi, K. B. Singh, S. K. Trigun, M. S. Hundal, D. S. Pandey, J. Organomet. Chem. 2016, 801, 68–79.
[48] S. Thangavel, M. Paulpandi, H. B. Friedrich, K. Murugan, S. Kalva, A. A. Skelton, J. Inorg. Biochem. 2016, 159, 50–61.
[49] R. P. Paitandi, R. K. Gupta, R. S. Singh, G. Sharma, B. Koch, D. S. Pandey, Eur. J. Med. Chem. 2014, 84, 17–29.
[50] R. K. Gupta, R. Pandey, G. Sharma, R. Prasad, B. Koch, S. Srikrishna, P.-Z. Li, Q. Xu, D. S. Pandey, Inorg. Chem. 2013, 52, 3687–3698.
[51] A. Petrini, R. Pettinari, F. Marchetti, C. Pettinari, B. Therrien, A. Galindo, R. Scopelliti, T. Riedel, P. J. Dyson, Inorg. Chem. 2017, 56, 13600–13612.
[52] R. Pettinari, F. Marchetti, C. Di Nicola, C. Pettinari, Eur. J. Inorg. Chem. 2018, 2018, 3521–3536.
[53] R. Lord, M. Zegke, I. R. Henderson, C. M. Pask, H. J. Shepherd, P. C. McGowan, Chemistry – A European Journal 2018, 0, DOI 10.1002/chem.201804901.

[54] I. Cassells, T. Stringer, A. T. Hutton, S. Prince, G. S. Smith, JBIC, J. Biol. Inorg. Chem. 2018, 23, 763–774.
[55] M. U. Raja, J. Tauchman, B. Therrien, G. Suss-Fink, T. Riedel, P. J. Dyson, Inorg. Chim. Acta 2014, 409, 479–483.
[56] G. Gupta, S. Cherukommu, G. Srinivas, S. W. Lee, S. H. Mun, J. Jung, N. Nagesh, C. Y. Lee, J. Inorg. Biochem. 2018, 189, 17–29.
[57] G. Gupta, A. Das, N. B. Ghate, T. Kim, J. Y. Ryu, J. Lee, N. Mandal, C. Y. Lee, Chem. Commun. (Cambridge, U. K.) 2016, 52, 4274–4277.
[58] G. Gupta, J. M. Kumar, A. Garci, N. Nagesh, B. Therrien, Molecules 2014, 19, 6031–6046, 16 pp.
[59] G. Gupta, J. Mahesh Kumar, A. Garci, N. Rangaraj, N. Nagesh, B. Therrien, ChemPlusChem 2014, 79, 610–618.
[60] G. Gupta, B. S. Murray, P. J. Dyson, B. Therrien, J. Organomet. Chem. 2014, 767, 78–82.
[61] L. Tabrizi, H. Chiniforoshan, Dalton Trans. 2017, 46, 2339–2349.
[62] J. M. Cross, N. Gallagher, J. H. Gill, M. Jain, A. W. McNeillis, K. L. Rockley, F. H. Tscherny, N. J. Wirszycz, D. S. Yufit, J. W. Walton, Dalton Trans. 2016, 45, 12807–12813.
[63] H. Pruchnik, M. Latocha, A. Zielinska, F. P. Pruchnik, J. Organomet. Chem. 2016, 822, 74–79.
[64] A. R. Burgoyne, C. H. Kaschula, M. I. Parker, G. S. Smith, Eur. J. Inorg. Chem. 2016, 2016, 1267–1273.
[65] G. Ludwig, I. Randelovic, D. Maksimovic-Ivanic, S. Mijatovic, M. Z. Bulatovic, D. Miljkovic, M. Korb, H. Lang, D. Steinborn, G. N. Kaluderovic, ChemMedChem 2014, 9, 1586–1593.
[66] S. Adhikari, O. Hussain, R. M. Phillips, W. Kaminsky, M. R. Kollipara, Appl. Organomet. Chem. 2018, 32, n/a.
[67] P. Starha, Z. Travnicek, B. Drahos, R. Herchel, Z. Dvorak, Appl. Organomet. Chem. 2018, 32, n/a.
[68] B. P. R. Aradhyula, M. Kalidasan, K. Gangele, D. K. Deb, S. L. Shepherd, R. M. Phillips, K. M. Poluri, M. R. Kollipara, ChemistrySelect 2017, 2, 2065–2076.
[69] C. M. Hackl, M. S. Legina, V. Pichler, M. Schmidlehner, A. Roller, O. Doemoetoer, E. A. Enyedy, M. A. Jakupec, W. Kandioller, B. K. Keppler, Chem. - Eur. J. 2016, 22, 17269–17281.
[70] W. Su, B. Peng, P. Li, Q. Xiao, S. Huang, Y. Gu, Z. Lai, Appl. Organomet. Chem. 2017, 31, n/a.
[71] N. Raja, N. Devika, G. Gupta, V. L. Nayak, A. Kamal, N. Nagesh, B. Therrien, J. Organomet. Chem. 2015, 794, 104–114.
[72] J. P. Johnpeter, G. Gupta, J. M. Kumar, G. Srinivas, N. Nagesh, B. Therrien, Inorg. Chem. 2013, 52, 13663–13673.
[73] G. Gupta, A. Garci, B. S. Murray, P. J. Dyson, G. Fabre, P. Trouillas, F. Giannini, J. Furrer, G. Suess-Fink, B. Therrien, Dalton Trans. 2013, 42, 15457–15463.
[74] A. R. Burgoyne, C. H. Kaschula, M. I. Parker, G. S. Smith, Eur. J. Inorg. Chem. 2017, 2017, 5379–5386.
[75] A. R. Burgoyne, C. H. Kaschula, M. I. Parker, G. S. Smith, J. Organomet. Chem. 2017, 846, 100–104.
[76] B. Basava Punna Rao A, A. Uma, T. Chiranjeevi, M. S. Bethu, J. Venkateswara Rao, D. K. Deb, B. Sarkar, W. Kaminsky, M. R. Kollipara, J. Organomet. Chem. 2016, 824, 131–139.
[77] N. R. Palepu, J. Richard Premkumar, A. K. Verma, K. Bhattacharjee, S. R. Joshi, S. Forbes, Y. Mozharivskyj, K. Mohan Rao, Arabian J. Chem. 2018, 11, 714–728.
[78] A. R. Burgoyne, B. C. E. Makhubela, M. Meyer, G. S. Smith, Eur. J. Inorg. Chem. 2015, 2015, 1433–1444.
[79] P. Chellan, K. M. Land, A. Shokar, A. Au, S. H. An, D. Taylor, P. J. Smith, T. Riedel, P. J. Dyson, K. Chibale, et al., Dalton Trans. 2014, 43, 513–526.
[80] J.-P. Tranchier, J. Dubarle-Offner, L. Peyroux, G. Gontard, T. Riedel, P. J. Dyson, H. Amouri, Synlett 2015, 26, 1563–1566.
[81] H. Amouri, J. Moussa, A. K. Renfrew, P. J. Dyson, M. N. Rager, L.-M. Chamoreau, Angew. Chem., Int. Ed. 2010, 49, 7530–7533.
[82] C. G. Hartinger, Angew. Chem., Int. Ed. 2010, 49, 8304–8305.
[83] T. Giraldi, G. Sava, G. Mestroni, G. Zassinovich, D. Stolfa, Chem.-Biol. Interact. 1978, 22, 231–8.
[84] G. Sava, S. Zorzet, L. Perissin, G. Mestroni, G. Zassinovich, A. Bontempi, Inorg. Chim. Acta 1987, 137, 69–71.
[85] G. Sava, T. Giraldi, G. Mestroni, G. Zassinovich, Chem.-Biol. Interact. 1983, 45, 1–6.
[86] P. V. Simpson, C. Schmidt, I. Ott, H. Bruhn, U. Schatzschneider, Eur. J. Inorg. Chem. 2013, 2013, 5547–5554.
[87] Y. Gothe, T. Marzo, L. Messori, N. Metzler-Nolte, Chem. Commun. (Cambridge, U. K.) 2015, 51, 3151–3153.
[88] Y. Gothe, T. Marzo, L. Messori, N. Metzler-Nolte, Chem. - Eur. J. 2016, 22, 12487–12494.
[89] E. Maftei, C. V. Maftei, P. G. Jones, M. Freytag, M. H. Franz, G. Kelter, H.-H. Fiebig, M. Tamm, I. Neda, Helv. Chim. Acta 2016, 99, 469–481.
[90] Y. Gothe, I. Romero-Canelon, T. Marzo, P. J. Sadler, L. Messori, N. Metzler-Nolte, Eur. J. Inorg. Chem. 2018, 2018, 2461–2470.
[91] U. Sliwinska-Hill, F. P. Pruchnik, M. Latocha, D. Nawrocka-Musial, S. Ulaszewski, Inorg. Chim. Acta 2013, 400, 26–31.
[92] A. Wilbuer, D. H. Vlecken, D. J. Schmitz, K. Kraeling, K. Harms, C. P. Bagowski, E. Meggers, Angew. Chem., Int. Ed. 2010, 49, 3839–3842, S3839/1-S3839/41.
[93] A. Kastl, A. Wilbuer, A. L. Merkel, L. Feng, P. Di Fazio, M. Ocker, E. Meggers, Chem. Commun. (Cambridge, U. K.) 2012, 48, 1863–1865.
[94] Z. Liu, L. Salassa, A. Habtemariam, A. M. Pizarro, G. J. Clarkson, P. J. Sadler, Inorg. Chem. 2011, 50, 5777–5783.
[95] Z. Liu, A. Habtemariam, A. M. Pizarro, G. J. Clarkson, P. J. Sadler, Organometallics 2011, 30, 4702–4710.
[96] Z. Liu, P. J. Sadler, Inorg. Chem. Front. 2014, 1, 668–672.

[97] K. K.-W. Lo, K. Y. Zhang, RSC Adv. 2012, 2, 12069–12083.
[98] A. J. Millett, A. Habtemariam, I. Romero-Canelón, G. J. Clarkson, P. J. Sadler, Organometallics 2015, 34, 2683–2694.
[99] Z. Liu, I. Romero-Canelon, A. Habtemariam, G. J. Clarkson, P. J. Sadler, Organometallics 2014, 33, 5324–5333.
[100] Y. Qi, Z. Liu, H. Li, P. J. Sadler, P. B. O'Connor, Rapid Commun. Mass Spectrom. 2013, 27, 2028–2032.
[101] H. Zhang, L. Guo, Z. Tian, M. Tian, S. Zhang, Z. Xu, P. Gong, X. Zheng, J. Zhao, Z. Liu, Chem. Commun. (Cambridge, U. K.) 2018, 54, 4421–4424.
[102] Z. Liu, I. Romero-Canelón, B. Qamar, J. M. Hearn, A. Habtemariam, N. P. E. Barry, A. M. Pizarro, G. J. Clarkson, P. J. Sadler, Angewandte Chemie International Edition 2014, 53, 3941–3946.
[103] J. M. Zimbron, K. Passador, B. Gatin-Fraudet, C.-M. Bachelet, D. Plazuk, L.-M. Chamoreau, C. Botuha, S. Thorimbert, M. Salmain, Organometallics 2017, 36, 3435–3442.
[104] J. Ruiz, V. Rodriguez, N. Cutillas, K. G. Samper, M. Capdevila, O. Palacios, A. Espinosa, Dalton Trans. 2012, 41, 12847–12856.
[105] V. Novohradsky, Z. Liu, M. Vojtiskova, P. J. Sadler, V. Brabec, J. Kasparkova, Metallomics 2014, 6, 682–690.
[106] G. S. Yellol, A. Donaire, J. G. Yellol, V. Vasylyeva, C. Janiak, J. Ruiz, Chem. Commun. (Cambridge, U. K.) 2013, 49, 11533–11535.
[107] J. Ruiz, C. Vicente, C. de Haro, D. Bautista, Inorg. Chem. 2013, 52, 974–982.
[108] J. Yellol, S. A. Perez, A. Buceta, G. Yellol, A. Donaire, P. Szumlas, P. J. Bednarski, G. Makhloufi, C. Janiak, A. Espinosa, et al., J. Med. Chem. 2015, 58, 7310–7327.
[109] S. Mukhopadhyay, R. K. Gupta, R. P. Paitandi, N. K. Rana, G. Sharma, B. Koch, L. K. Rana, M. S. Hundal, D. S. Pandey, Organometallics 2015, 34, 4491–4506.
[110] Z. Mou, N. Deng, F. Zhang, J. Zhang, J. Cen, X. Zhang, Eur. J. Med. Chem. 2017, 138, 72–82.
[111] L. C. Sudding, R. Payne, P. Govender, F. Edafe, C. M. Clavel, P. J. Dyson, B. Therrien, G. S. Smith, J. Organomet. Chem. 2014, 774, 79–85.
[112] F. Schmitt, K. Donnelly, J. K. Muenzner, T. Rehm, V. Novohradsky, V. Brabec, J. Kasparkova, M. Albrecht, R. Schobert, T. Mueller, J. Inorg. Biochem. 2016, 163, 221–228.
[113] W. Su, X. Wang, X. Lei, Q. Xiao, S. Huang, P. Li, J. Organomet. Chem. 2017, 833, 54–60.
[114] Y. Han, Z. Tian, S. Zhang, J. Li, Y. Li, Y. Liu, M. Gao, X. Liu, Z. Liu, J Inorg Biochem 2018, 189, 163–171.
[115] Y. Yang, L. Guo, Z. Tian, Y. Gong, H. Zheng, S. Zhang, Z. Xu, X. Ge, Z. Liu, Inorg. Chem. 2018, 57, 11087–11098.
[116] Y. Han, X. Liu, Z. Tian, X. Ge, J. Li, M. Gao, Y. Li, Y. Liu, Z. Liu, Chem Asian J 2018.
[117] Y. Zhang, S. Zhang, Z. Tian, J. Li, Z. Xu, S. Li, Z. Liu, Dalton Trans. 2018, 47, 13781–13787.
[118] S. C. Larnaudie, J. C. Brendel, I. Romero-Canelon, C. Sanchez-Cano, S. Catrouillet, J. Sanchis, J. P. C. Coverdale, J.-I. Song, A. Habtemariam, P. J. Sadler, et al., Biomacromolecules 2018, 19, 239–247.



Organometallic iridium compounds: the effects of *C*-donor ligands on anticancer activity

To date, the most effective iridium anticancer compounds are those with "piano-stool" structures and which usually incorporate a variety of *N*-, *O*-, *S*- and *P*- bidentate ligands. These compounds can be easily functionalized by changing the bidentate ligands, the ancillary ligands and increasing the aromaticity of the arene substituent, all in the hope to optimize their activities and allow the determination of structure activity relationships. However, research towards *C*-donor ligands has only just emerged in the past 5 years, with cyclometalated and *N*-heterocyclic carbene iridium complexes showing significant increases in potency towards a range of cancer cell lines. This mini-review highlights the recent and ongoing research in *C*-donor iridium organometallic complexes, and herein we discuss their importance as potential anticancer drugs.

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